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Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis

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ABSTRACT

Objectives: To quantitatively assess time-series studies of daily nitrogen dioxide (NO_2) and mortality and hospital admissions which also controlled for particulate matter (PM) to determine whether or to what extent the NO_2 associations are independent of PM.

Design: A systematic review and meta-analysis.

Methods: Time-series studies—published in peer-reviewed journals worldwide, up to May 2011—that reported both single-pollutant and two-pollutant model estimates for NO_2 and PM were ascertained from bibliographic databases (PubMed, EMBASE and Web of Science) and reviews. Random-effects summary estimates were calculated globally and stratified by different geographical regions, and effect modification was investigated.

Outcome measures: Mortality and hospital admissions for various cardiovascular or respiratory diseases in different age groups in the general population.

Results: 60 eligible studies were identified, and meta-analysis was conducted on 23 outcomes. Two-pollutant model study estimates generally showed that the NO_2 associations were independent of PM mass. For all-cause mortality, a 10 µg/m^3 increase in 24-hour NO_2 was associated with a 0.78% (95% CI 0.47% to 1.09%) increase in the risk of death, which reduced to 0.60% (0.33% to 0.87%) after control for PM. Heterogeneity between geographical region-specific estimates was removed by control for PM (I^2 from 66.9% to 0%). Estimates of PM and daily mortality assembled from the same studies were greatly attenuated after control for NO_2: from 0.51% (0.29% to 0.74%) to 0.18% (−0.11% to 0.47%) per 10 µg/m^3 PM_{10} and 0.74% (0.34% to 1.14%) to 0.54% (−0.25% to 1.34%) for $PM_{2.5}$.

Conclusions: The association between short-term exposure to NO_2 and adverse health outcomes is largely independent of PM mass. Further studies should attempt to investigate whether this is a generic PM effect or whether it is modified by the source and physicochemical characteristics of PM. This finding strengthens the argument for NO_2 having a causal role in health effects.

Strengths and limitations of this study

- This is, to date, the most comprehensive quantitative systematic review of the time-series literature on nitrogen dioxide (NO_2) published worldwide to evaluate the two-pollutant model estimates of mortality or hospital admissions and short-term exposure to NO_2 adjusted for particulate air pollution.
- It reports meta-analytical estimates both globally and for different geographical regions, as well as provides an assessment of heterogeneity between the region-specific estimates.
- The protocol-led approach to the identification of studies and estimates for use in meta-analysis minimised selection bias at each stage of the review.
- Meta-analysis was limited to studies that provided effect estimates in numerical—rather than graphical—form, along with sufficient quantitative data to enable standardisation of estimates.
- Further work is needed to understand reasons for the heterogeneity observed and to quantitatively assess the extent to which PM may be associated with health independently of NO_2.

INTRODUCTION

Outdoor air pollution has long been established as a hazard to human health, with particulate matter (PM) regarded as the most plausible toxicant in the mixture of ambient air pollutants.[1–5] The epidemiological evidence has consistently shown adverse associations between chronic and short-term exposure to PM and mortality and morbidity from cardiovascular and respiratory disease, and this is supported by experimental evidence.[6] While the epidemiological evidence also shows relationships between nitrogen dioxide (NO_2) and adverse health effects, concerns have been expressed repeatedly about the causal nature of these associations.[7–11] It has been asserted

that the NO_2 associations do not reflect adverse effects of NO_2 itself but, rather, reflect the health effects of other air pollutants, mainly PM or other components of the complex mixture of traffic-related air pollutants. Primarily, this is due to the strong correlations between NO_2 and other combustion-derived air pollutants, especially PM. The extent of these correlations varies from city-to-city and over time, due to variations in emission sources. Scepticism also exists because of limited experimental evidence (controlled human exposure and animal toxicology studies) for NO_2, which, to date, has focused largely on respiratory endpoints and has generally employed concentrations of NO_2 well above current ambient levels.[7–9] In light of the uncertainties regarding NO_2 and the stronger evidence for associations between PM and health, many researchers and policymakers have adopted a view that the epidemiological associations of NO_2 reflect adverse health effects of PM.

In an earlier paper, we reviewed the time-series evidence associating daily concentrations of NO_2 with daily mortality and emergency hospital admissions.[12] In this study, we assess the subset of time-series studies, reporting all-year estimates of NO_2 from both single-pollutant and two-pollutant models adjusted for PM to determine whether the NO_2 associations are attenuated after adjustment for PM.

METHODS

The full method and a priori protocols governing the identification of studies and effect estimates for the systematic review have been described previously,[12–14] but a synopsis, along with aspects unique to this review, is provided below.

Identification of studies for review

Three bibliographic databases were searched to identify peer-reviewed time-series studies of NO_2 and daily mortality or hospital admissions indexed up to May 2011. No restriction on language was applied. The literature search strategy is described in the online supplementary material, and the following inclusion criteria were used: papers must (1) have had a minimum of 1 year of data; (2) been based on the general population; (3) have controlled for important confounding factors, including season and meteorological factors; and (4) have reported sufficient quantitative information, in numeric format, to enable the calculation of standardised effect estimates and standard errors for use in quantitative analysis. Two authors of the review—ICM and RWA—undertook the literature search.

Data extraction and coding

Data from each relevant study were entered into a Microsoft Access database (Microsoft Office 2010, Microsoft Corporation). These included:

A. Citation details of each paper;
B. All-year single-pollutant and two-pollutant model estimates of NO_2 adjusted for PM;
C. Single-pollutant and two-pollutant model estimates of PM adjusted for NO_2 reported in studies providing data for NO_2;
D. Season-specific estimates of NO_2, including those adjusted for PM, from studies reporting all-year estimates;
E. Descriptive (outcome, diagnosis (International Classification of Diseases codes), age, etc) and quantitative data (pollution increment and averaging time etc) associated with each estimate, and needed for calculating standardised estimates expressed as the percentage change (and 95% CI) in the mean number of daily events associated with a 10 $\mu g/m^3$ increase in NO_2 (or PM);
F. Correlations between concentrations of NO_2 and PM;
G. Effect modifiers for investigating of sources of heterogeneity in all-year estimates.

Time-series studies often report results for different time lags (in days) between exposure and health events, and they vary in the lag for the reported results. We identified, for each outcome/disease/age/averaging time combination from each study, a pair of estimates of NO_2, that is from a single-pollutant model and a corresponding estimate adjusted for PM for the same lag, to enable comparison of the NO_2 association before and after adjustment for PM. To avoid selection bias, we developed an a priori protocol for identifying the principal lag for each outcome/disease/age/averaging time combination for use in our review. This was the lag highlighted by the author or stated a priori, and if this was not clear, because several lagged model estimates were reported, we chose (1) the lag with the highest statistical significance, regardless of the estimate being positive or negative, or (2) the lag with the largest estimate, again, irrespective of its direction. If only results from cumulative or distributed lag models—that is, lags averaged over several days—were reported in a study, these were used. In some instances, a different lag was investigated in two-pollutant models. In such cases, the lagged estimate from the two-pollutant model was coded according to the same algorithm and the (additional) corresponding single-pollutant estimate for the same lag was coded in our database.

Processing of data also included classifying each study into the geographical region, as the WHO region, in which the study was conducted, as well as categorising the various metrics of PM controlled for in two-pollutant models: see online supplementary material for details.

Statistical analyses

A similar procedure to that outlined in our earlier paper was used for meta-analysis,[12] but with some modifications, in order to identify a pair of estimates of NO_2 for each pollutant/outcome combination from each study. We applied an a priori protocol to select estimates for meta-analysis to avoid selection bias and duplication of studies from the same population. We gave priority to

estimates from multicity studies over estimates from single-city studies and the results from any one city appeared only once in a meta-analysis. If results from more than one multicity study within a WHO region were available, we selected, in order of priority, the multicity estimate from the study: (1) with the most cities/greatest geographical coverage; (2) the most recently published; (3) the most recent study time period. If a multicity study did not report a summary estimate across the cities examined, for analysis, we treated estimates from these studies in the same manner as estimates from single-city studies. We selected estimates from single-city studies only if they did not appear in multicity studies. For cities not included in a multicity study summary result, we selected, in order of priority: (1) the most recently published, or (2) the most recent study time period.

Meta-analysis was conducted when ≥4 estimates were available for an outcome/disease/age/averaging time combination—including where a multicity estimate was available—and summary estimates were calculated using a random-effects model.[15] We used a staged approach to meta-analysis, with single-city estimates pooled within WHO region prior to the pooled single-city and selected multicity estimates being pooled to produce a global estimate and WHO region-specific summary estimates. Heterogeneity between WHO region summary estimates was assessed using the I^2 statistic,[16] with I^2 statistics >50% regarded as being evidence of high heterogeneity.[17]

Meta-analysis was undertaken for:

A. Single-pollutant NO_2 estimates relating to two-pollutant models;
B. Corresponding NO_2 estimates adjusted for any PM metric:
   i. if within a study, several estimates of NO_2 adjusted for different individual PM metrics were available, a NO_2 estimate was selected according to the following order of priority of PM metric used in adjustment: PM_{10}, $PM_{2.5}$, Black Smoke, $PM_{10-2.5}$;
   ii. if, having applied the protocol, a NO_2 estimate was not selected for a city because several were available due to different PM metrics used to adjust the NO_2 effect in different studies, the NO_2 estimate was chosen in the order of priority of the PM metrics listed above.
C. We conducted additional meta-analyses for NO_2 adjusted for specific metrics of particles, for example, NO_2 adjusted for PM_{10} and separately for $PM_{2.5}$, and so on, to determine whether the NO_2 associations showed different sensitivity to control for different PM metrics.

All analyses were conducted in STATA (STATA/SE V.11. StataCorp, Texas, USA).

RESULTS

Sixty studies provided estimates of both (1) NO_2, single-pollutant, and (2) NO_2 adjusted for PM: a list of references is provided in the online supplementary material. Table 1 presents a summary of these 60 time-series studies stratified by the PM metric controlled for in regression models, broad disease categories, WHO regions in which the studies were conducted, single-city and multicity study designs, and by averaging time (24-hour and 1 hour).

There were 36 and 24 studies of daily mortality or hospital admissions, respectively, and 13 studies used a multicity design. The majority of the studies were conducted in the WHO regions European A and Western Pacific region B, and most used 24-hour NO_2. Forty of the 60 studies controlled for the effects of daily PM_{10} in the regression models for NO_2, and a much smaller number of studies used other particle size fractions or constituents of PM. Eight studies of mortality and two of hospital admissions reported estimates of NO_2, each adjusted for a different PM metric. None of the studies investigated the influence of carbon on the NO_2 associations, and four studies controlled for the effects of ultrafine particles.

NO_2 and all-cause mortality

Figure 1 shows all available (32 pairs) single-pollutant and two-pollutant estimates for 24-hour NO_2 and daily all-cause mortality in all ages. In the majority of studies, daily NO_2 was positively and significantly associated with increases in the risk of death, including after controlling for daily PM. In many of the studies, the NO_2 estimates were not greatly reduced in size, changed direction or lose statistical significance after adjustment for PM. In general, the NO_2 estimates appeared robust to adjustment for PM at both high and low correlations between concentrations of NO_2 and PM.

Fifteen (of 32) pairs of estimates for 24-hour NO_2 and all-cause mortality, which represented 26 cities from five WHO regions, were selected for meta-analysis (see online supplementary figure S1). The random-effects single-pollutant summary estimate for all-cause mortality was 0.78% (95% CI 0.47% to 1.09%) per 10 µg/m^3 increase in NO_2. There was evidence of high heterogeneity (I^2=66.9%) between the WHO region-specific estimates, which ranged from 0.48% for WHO region America A to 1.41% for South East Asia B (see online supplementary table S1). The overall estimate was comparable to the single-pollutant summary estimate of 0.71% (95% CI 0.43% to 1.00%) calculated from the larger body of time-series evidence analysed in our previous paper.[12] After adjustment for daily PM, all-cause mortality remained positively and significantly associated with 24-hour NO_2: 0.60% (95% CI 0.33% to 0.87%) per 10 µg/m^3 increase in NO_2, and there was no evidence of heterogeneity (I^2=0%) between the region-specific estimates.

Control for specific PM metrics did not greatly alter the relationship of 24-hour NO_2 with all-cause mortality (table 2). With the exception of NO_2 adjusted for PM_{10}, and to a lesser extent $PM_{2.5}$, meta-analyses for NO_2 adjusted for the remaining PM metrics were limited to

Table 1 Summary of time-series studies of daily mortality or hospital admissions and NO_2 adjusted for PM

	Total		Multicity study		Single-city study	
Outcome	Mortality	Hospital admissions	Mortality	Hospital admissions	Mortality	Hospital admissions
Total	36	24	9	4	27	20
NO_2+PM*						
PM_{10}	23	17	6	2	17	15
$PM_{2.5}$	7	1	3	1	4	0
$PM_{10-2.5}$	4	0	3	0	1	0
BS	5	4	3	2	2	2
PNC	3	1	0	0	3	1
Carbon	0	0	0	0	0	0
TSP	4	2	0	1	4	1
Visibility	2	1	2	1	0	0
>1 PM metric	0	1	0	0	0	1
Disease†						
All-cause	27	1	7	0	20	1
Cardiovascular	17	11	4	2	13	9
Respiratory	7	17	3	3	4	14
WHO region‡						
American A	8	4	3	0	5	4
European A	9	12	3	2	6	10
Western Pacific B	14	5	2	0	12	5
American B	4	2	0	0	4	2
Western Pacific A	1	2	1	2	0	0
South East Asia B	2	0	2	0	0	0
Averaging time						
24 hour	29	21	6	3	23	18
Maximum 1 hour	7	5	3	2	4	3

*The eight categories of PM metrics listed in the table above have been generated by grouping different measures of particles. PM_{10} and $PM_{2.5}$ refer to the mass per cubic metre of particles of generally <10 μm and 2.5 μm diameter, respectively, in the ambient air.
†Respiratory includes all-respiratory diseases, asthma, COPD, COPD including asthma, lower respiratory infections and upper respiratory diseases; Cardiovascular includes all-cardiovascular diseases, cardiac disease, heart failure, ischaemic heart disease, dysrhythmia and stroke.
‡WHO regions: (A) very low child and adult mortality; (B) low child mortality and low adult mortality; (C) low child mortality and high adult mortality; (D) high child mortality and high adult mortality.
BS, Black Smoke; COPD, chronic obstructive pulmonary disease; PM, particulate matter; PNC, particle number concentration; TSP, total suspended particles.

findings from a multicity Canadian study by Burnett *et al*[18]—see figure 1.

Six pairs of estimates were available for meta-analysis for all-cause mortality and 1 hour NO_2 adjusted for PM (see online supplementary figure S2). Thirty of the 36 cities represented by these estimates were in Europe. Meta-analysis of four pairs of estimates resulted in an overall estimate of 0.32% (95% CI −0.02% to 0.66%) for a 10 μg/m^3 increment in 1 hour NO_2 and 0.20% (95% CI −0.24% to 0.65%) following adjustment for PM (see online supplementary table S2). High heterogeneity was observed between the WHO region-specific estimates. In contrast with findings for 24-hour measures, the summary estimate for 1 hour NO_2 for WHO region European A was little affected by adjustment for PM_{10} (or Black Smoke)—see online supplementary table S2. Table 3 provides meta-analysis results for all-cause mortality and 1 hour NO_2 adjusted for different PM metrics. Control for PM_{10} led to attenuation of the estimate and loss of statistical significance, while the association was robust to control for Black Smoke and visibility (measured as black suspended particles, BSP).

NO_2 and mortality from specific causes

NO_2 estimates adjusted for PM were available for several specific causes of death in all ages: all cardiovascular (see online supplementary figures S3 and S4), all respiratory (see online supplementary figure S5), stroke (see online supplementary figure S6), cardiac (see online supplementary figure S7), ischaemic heart disease, dysrhythmia, chronic obstructive pulmonary disease including asthma and lower respiratory infections (see online supplementary figure S8). Sufficient numbers of estimates for meta-analysis were available for all cardiovascular (see online supplementary table S3), all respiratory (see online supplementary table S4) and stroke (see online supplementary table S5) mortality.

Eight studies providing 14 pairs of estimates showed positive associations between all cardiovascular deaths and 24-hour NO_2, including after adjustment mainly for PM_{10} (see online supplementary figure S3). However,

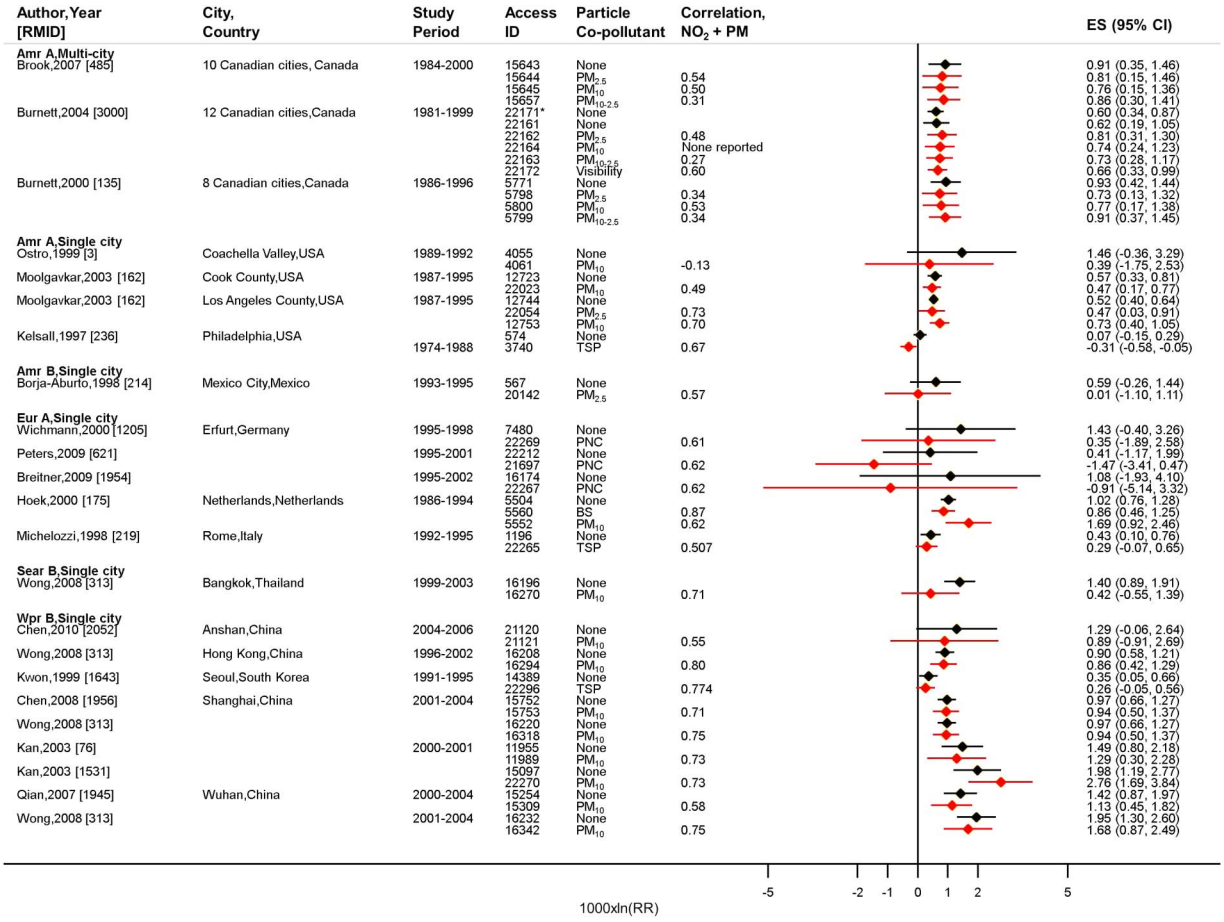

Figure 1 All available studies providing two-pollutant model estimates for meta-analysis for all-cause mortality, all ages, 24-hour NO_2. 1000×ln (RR) approximates to a percentage change per 10 µg/m^3. *Single-pollutant model estimate for days with both NO_2 and visibility (coefficient of haze, COH) data in Burnett *et al*,[18] [RMID 3000]. NO_2, single-pollutant NO_2 adjusted for PM.

attenuation of estimates and loss of statistical significance was observed in the few studies with control for $PM_{2.5}$ or Black Smoke. Meta-analysis of 10 pairs of estimates found a 1.07% (95% CI 0.43% to 1.72%) increase in the risk of death from all cardiovascular diseases per 10 µg/m^3 increase in 24-hour NO_2 (see online supplementary table S3 and figure S9). This was attenuated (0.82% (95% CI 0.22% to 1.42%))—see online supplementary table S3—following adjustment for PM, but comparable to our earlier result (0.88% (95% CI 0.63% to 1.13%)).[12] Control of the NO_2 association with all cardiovascular mortality for specific PM metrics showed an association that was robust to adjustment for PM_{10} (table 2). There were too few estimates to permit meta-analysis for other PM metrics controlled for in the studies. The available data for 1 hour NO_2 and all cardiovascular mortality were sparse and limited to two studies representing 29 European cities that showed positive NO_2 associations that were robust to adjustment for both PM_{10} and Black Smoke (see table 3 and online supplementary figure S4).

Evidence for all respiratory mortality and 24-hour NO_2 adjusted for PM came from six cities (see online supplementary figure S5). Meta-analysis produced a 1.42% (95% CI 0.64% to 2.21%) increased risk of all respiratory deaths per 10 µg/m^3 increase in 24-hour NO_2 (see online supplementary table S4 and figure S10). The corresponding estimate adjusted for particles was attenuated (1.13% (95% CI 0.46% to 1.81%)) but was comparable to the single-pollutant estimate (1.09% (95% CI 0.75% to 1.42%)) derived from the larger body of time-series evidence examined in our previous paper.[12] There was no evidence of heterogeneity (I^2=0%) between the geographic specific estimates either before or after adjustment for PM (see online supplementary table S4). Evidence for associations between all respiratory mortality and 1 hour NO_2 came solely from the multicity APHEA II study of 29 European cities,[19] which showed a positive association that was robust to adjustment for PM_{10} but not Black Smoke (table 3).

PM and mortality

Meta-analyses were undertaken separately for PM adjusted for the different averaging times of NO_2 to allow comparison with the relevant meta-analyses for NO_2, using data from the same studies, cities and time periods. Figure 2 shows positive, single-pollutant

Table 2 Random-effects summary estimates (as percentage change (95% CIs)) for mortality or hospital admissions associated with a 10 μg/m^3 increase 24 hour average pollution

	All SC/MC*	Selected SC/MC (cities)†	24-hour NO_2		24-hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	13/3	4/1 (21)	0.92 (0.58 to 1.72)	0.85 (0.52 to 1.18)	0.51 (0.29 to 0.74)	0.18 (−0.11 to 0.47)
$PM_{2.5}$	2/3	2/1 (14)	0.53 (0.42 to 0.64)	0.57 (0.24 to 0.89)	0.74 (0.34 to 1.14)	0.54 (−0.25 to 1.34)
$PM_{10-2.5}$	0/3	0/1 (12)	0.62 (0.19 to 1.06)	0.73 (0.28 to 1.18)	0.65 (−0.10 to 1.42)	0.31 (−0.49 to 1.11)
Visibility	0/1	0/1 (12)	0.60 (0.34 to 0.87)	0.66 (0.33 to 1.00)	40.93 (23.39 to 60.97)‡	12.42 (−4.47 to 32.29)‡
All cardiovascular mortality, all ages						
PM_{10}	10/0	4/0 (8)	0.99 (0.49 to 1.49)	0.87 (0.28 to 1.46)	0.48 (0.18 to 0.78)	0.19 (−0.21 to 0.59)
All respiratory mortality, all ages						
PM_{10}	7/0	2/0 (5)	1.44 (0.63 to 2.27)	1.15 (0.47 to 1.84)	0.58 (0.22 to 0.93)	0.13 (−0.18 to 0.44)
All respiratory hospital admissions, children (5–14 years)						
PM_{10}	0/1	0/1 (5)	5.95 (1.74 to 10.33)	6.56 (3.08 to 10.17)	–	–
Cardiac hospital admissions, all ages						
PM_{10}	2/1	2/1 (7)	0.93 (0.46 to 1.40)	0.75 (−0.13 to 1.64)	–	–
BS	0/1	0/1 (4)	0.68 (0.17 to 1.20)	0.36 (−0.65 to 1.38)	–	–
TSP	0/1	0/1 (6)	1.03 (0.45 to 1.61)	1.08 (0.43 to 1.72)	–	–

*Numbers of available pairs of single-city (SC)/multi-city (MC) estimates from all studies.
†Numbers of pairs of pooled (from single-city estimates) and multicity estimates used to calculate the overall summary estimate across WHO regions. Estimates were selected for meta-analysis from all those available. The number of cities represented by the summary estimates is given in brackets.
‡The results for visibility (measured as coefficient of haze (COH units)) are not comparable to other PM results.
BS. Black Smoke; NO_2, nitrogen dioxide; PM, particulate matter.

Table 3 Random-effects summary estimates (as percentage change (95% CIs)) for mortality or hospital admissions associated with a 10 μg/m^3 increase in air pollution

	All SC/MC*	Selected SC/MC (cities)†	1 hour NO_2		24-hour PM	
			Single-pollutant	Adjusted for PM	Single-pollutant	Adjusted for NO_2
All-cause mortality, all ages						
PM_{10}	2/1	2/1 (32)	0.22 (−0.15 to 0.60)	0.10 (−0.40 to 0.61)	0.52 (0.29 to 0.75)	0.48 (0.31 to 0.66)
BS	0/2	0/1 (30)	0.30 (0.22 to 0.38)	0.33 (0.23 to 0.43)	0.60 (0.30 to 0.90)	0.26 (0.00 to 0.52)
Visibility	0/1	0/1 (4)	0.63 (0.21 to 1.05)	0.52 (0.05 to 1.00)	35.70 (3.97 to 77.12)‡	10.24 (−20.03 to 51.97)‡
All cardiovascular mortality, all ages						
PM_{10}	1/1	0/1 (29)	0.40 (0.29 to 0.51)	0.35 (0.21 to 0.49)	0.76 (0.47 to 1.05)	0.32 (0.05 to 0.59)
BS	1/1	0/1 (29)	0.40 (0.29 to 0.51)	0.44 (0.31 to 0.57)	0.62 (0.35 to 0.90)	0.17 (−0.10 to 0.44)
All respiratory mortality, all ages						
PM_{10}	0/1	0/1 (29)	0.38 (0.17 to 0.59)	0.37 (0.08 to 0.66)	0.71 (0.22 to 1.20)	0.20 (−0.29 to 0.69)
BS	0/1	0/1 (29)	0.38 (0.17 to 0.59)	0.26 (−0.12 to 0.64)	0.84 (0.11 to 1.58)	0.57 (−0.34 to 1.48)
All respiratory hospital admissions, children (<5 years)						
PM_{10}	1/1	1/1 (6)	0.77 (−0.59 to 2.15)	0.13 (−0.09 to 0.35)	–	–
$PM_{2.5}$	0/1	0/1 (4)	1.62 (0.41 to 2.84)	4.85 (0.41 to 9.50)	–	–
All respiratory hospital admissions, elderly (65+years)						
Visibility	0/1	0/1 (4)	1.42 (0.79 to 2.06)	1.21 (0.47 to 1.95)	–	–
Cardiac hospital admissions, elderly						
Visibility	0/1	0/1 (4)	1.21 (0.84 to 1.58)	0.73 (0.31 to 1.16)	–	–

*Numbers of available pairs of single-city (SC)/multi-city (MC) estimates from all studies.
†Numbers of pairs of pooled (from single-city estimates) and multicity estimates used to calculate the overall summary estimate across WHO regions. Estimates were selected for meta-analysis from all those available. The number of cities represented by the summary estimates is given in brackets.
‡The results for visibility (measured as black suspended particles (10^{-4}/m)) are not comparable to other PM results.
BS, Black Smoke; NO_2, nitrogen dioxide; PM, particulate matter.

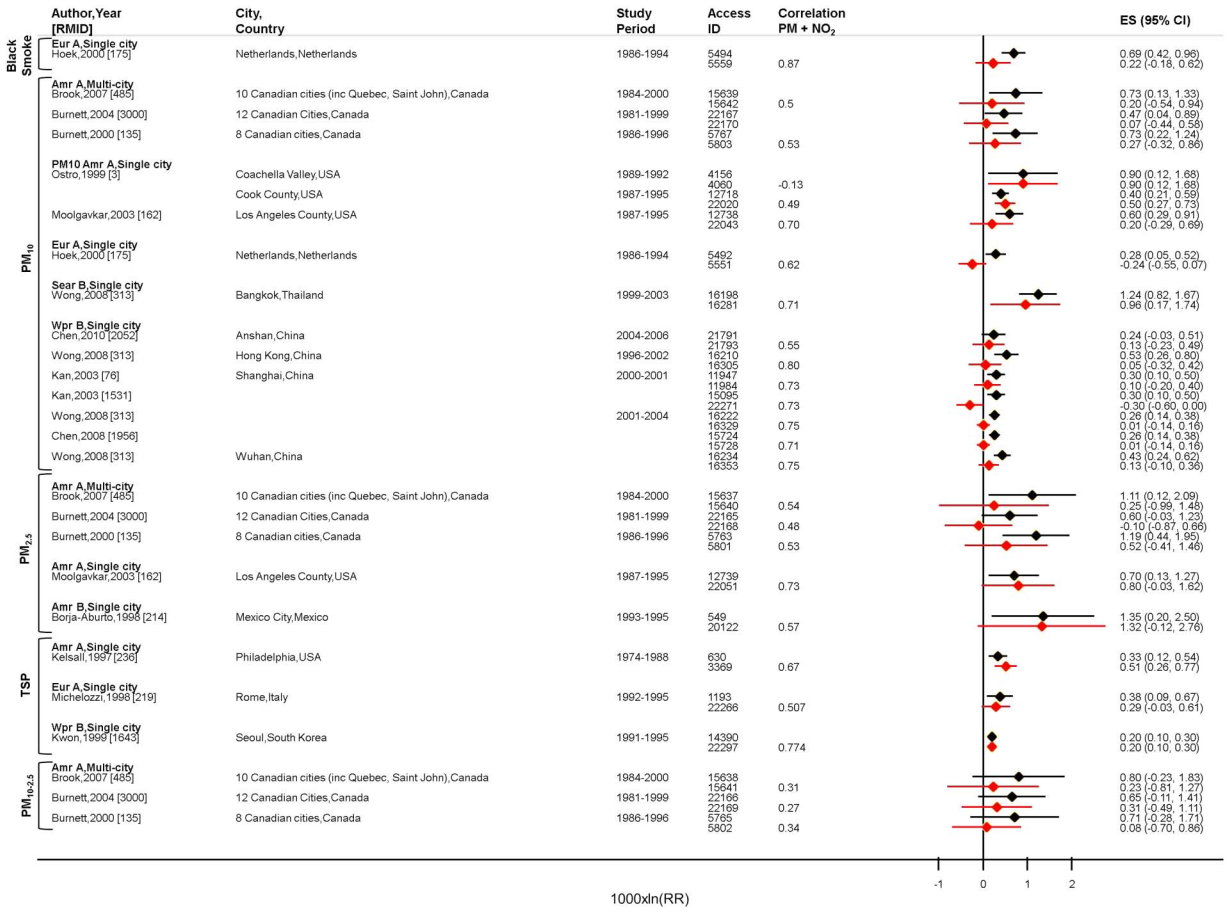

Figure 2 All studies providing two-pollutant model estimates for all-cause mortality, all ages, PM adjusted for 24-hour NO_2. PM, particulate matter. PM, single-pollutant PM adjusted for NO_2.

associations between various mass metrics of PM and all-cause mortality. In the majority of studies, attenuation of estimates was observed following control for 24-hour NO_2. Estimates for ultrafine particles and all-cause mortality were robust to adjustment for 24-hour NO_2 (see online supplementary figure S11), but the data came from three studies conducted in the same city—Erfurt, Germany. Results of meta-analysis for all-cause mortality and PM metrics are shown in tables 2 and 3 for adjustment for 24-hour and 1 hour NO_2, respectively. In contrast to the results for NO_2, the summary estimates for PM were attenuated, in most cases by more than half, and CIs overlapped zero. Evidence of high heterogeneity between region-specific summary estimates for PM_{10} and all-cause mortality was identified (see online supplementary table S6). Summary estimates for deaths from all cardiovascular or all respiratory diseases and PM were also sensitive to control for NO_2 (see tables 2 and 3; study estimates in online supplementary figures S12, S13, tables S7 and S8 for region-specific results).

NO_2 and hospital admissions

Few cause-specific and age-specific combinations of hospital admissions for 24-hour or 1 hour NO_2 with control for PM had sufficient numbers of estimates for meta-analysis—all respiratory diseases in children and the elderly, asthma in children, and cardiac disease in all ages and the elderly—and half were based solely on a multicity estimate from a single study.

Positive associations were identified between all respiratory hospital admissions in different age groups and 24-hour or 1 hour NO_2, which remained after control for PM (see tables 2 and 3; online supplementary figures S14 and S15 for available study estimates).

Evidence for the association between hospitalisation for asthma in different ages and daily NO_2 adjusted for PM came from seven studies (see online supplementary figures S16 and S17), six of which were conducted in Europe. Sufficient estimates for meta-analysis were only available for asthma admissions in children and 24-hour NO_2 adjusted for any particles (measured as Black Smoke, PM_{10} and PNC): a 2.81% (95% CI −1.28% to 7.06%) increase in risk per 10 µg/m^3 24-hour NO_2 was attenuated following adjustment for particles (2.24% (95% CI −1.12% to 5.71%)).

Five studies provided evidence for the relationship between 24-hour NO_2 adjusted for PM and hospitalisation for cardiac disease in all ages (see online supplementary figure S18) and the elderly (see online supplementary figure S19). Meta-analysis for the all age

category (table 2) identified positive estimates that were attenuated and CIs overlapped zero after controlling for PM_{10} and Black Smoke. One multicity study of four Australian cities provided evidence for the relationship between 1 hour NO_2 and cardiac admissions in the elderly. The association (1.21% (95% CI 0.84% to 1.58%)) was weakened by control for BSP (an indicator of fine particles), but remained statistically significant (0.73% (95% CI 0.31% to 1.16%)).

Sources of variation in NO_2 estimates

We examined season-specific NO_2 estimates of mortality from studies that reported all-year estimates to explore possible effect modification by season. Some studies, mainly from Western Europe, Canada and the USA, reported stronger associations between daily mortality and NO_2 in the summer months (see online supplementary figures S20–S22). The extent of the correlations between concentrations of NO_2 and PM in the different seasons is unclear because very few studies reported these data, and only one study reported season-specific estimates adjusted for PM. Similarly, limited evidence is available on which to base an assessment of seasonal variation of associations between hospitalisation for cardiovascular and respiratory diseases and 24-hour NO_2 (see online supplementary figure S23).

We explored reasons for the observed high heterogeneity by ranking study estimates for all-cause mortality and 24-hour NO_2 (from the full data set)[12] by different potential effect modifiers (see online supplementary figures S24–S27). None of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the observed between-study variability.

DISCUSSION

Sixty time-series studies of NO_2 were used to determine whether NO_2 is associated with daily mortality or hospital admissions independently of daily PM. In general, our results demonstrate that after controlling for PM, daily NO_2 remained significantly associated with increases in the risk of adverse health outcomes. The evidence appears clearest for daily deaths from all causes and from all cardiovascular and all respiratory diseases, and for all respiratory hospital admissions, outcomes for which more co-pollutant estimates were available. Robustness of the NO_2 associations to control for PM was observed at both high and low correlations between NO_2 and PM, and no clear relationship could be discerned between the correlations and changes in the size of the adjusted NO_2 estimates. In contrast to the results for NO_2, the associations between daily PM and the main mortality outcomes (all cause, all cardiovascular, all respiratory) were very sensitive to the inclusion of NO_2 in two-pollutant models.

Two/multipollutant models are increasingly being used to draw conclusions about whether or not NO_2 is independently associated with adverse health outcomes. This comprehensive review provides systematic evaluation and formal meta-analysis of the full body of two-pollutant estimates of NO_2 adjusted for PM, across several cause-specific and age-specific health outcomes, both globally and by different geographical regions. While earlier reviews[7–8 13 20–23] included some assessment of these data, they were either limited in scope to specific health outcomes, and/or examined two-pollutant and multipollutant model NO_2 estimates together, or did not undertake meta-analysis whatsoever. Another key strength of this review is the protocol-led approach to identifying and assembling studies and estimates, which aimed to minimise selection bias in the different stages of the review.

The subset of studies of NO_2 analysed in this paper were generally comparable to the studies examined in our earlier paper in terms of the magnitudes of summary estimates and overlap in CIs.[12] For example, the single-pollutant summary estimates for all-cause mortality, the outcome with the most data, were similar across both data sets, suggesting that the studies reporting two-pollutant model estimates were typical of the wider body of time-series evidence of NO_2.

While evidence of NO_2 associations which are robust to control for PM mass has been identified, it is possible that there may be some residual confounding by PM. The components of PM—primary combustion particles, for example, ultrafine particles or Black Carbon—which have been proposed as the real causal agents of the NO_2 associations, were not included in co-pollutant models of NO_2 because concentration data for these pollutants were either unavailable or sparse, reflecting the fact that these PM metrics are not routinely measured. PM_{10} was by far the most used metric— in 67% of the studies. Summary estimates of NO_2 were generally robust to adjustment for PM_{10}. However, PM_{10} may not adequately reflect the toxic component of PM because it reflects a number of sources that do not include combustion/traffic and that, are not shared with NO_2. Where the data permitted meta-analysis, robustness of the NO_2 associations to adjustment for $PM_{2.5}$ and Black Smoke was observed. Few data were available to permit an assessment of the extent to which the NO_2 associations are sensitive to control for combustion-derived particles such as Black Carbon or ultrafine particles. This has also been noted by others.[7–8 24]

Given that the sources and composition of PM vary by location, and hence its toxicity, it cannot be assumed that PM represents the same thing in each study (city/country). In view of the differential toxicity of PM, it is preferable to examine individual studies that used more than one particle metric to investigate possible confounding of the NO_2 associations by PM when answering the research question, because they 'tested' the robustness of the NO_2 associations to different fractions/components of the ambient aerosol in the same location.

Unfortunately, such studies were few in number (8), but their findings support the view that the associations of NO_2 with major health outcomes are robust to adjustment for PM measured in different ways.

We observed confounding of the associations between daily PM and mortality outcomes by NO_2. This suggests that NO_2, rather than the PM metrics examined, is a better predictor of the observed mortality effects in the cities examined. An alternative interpretation may be that daily variation in NO_2 in the cities better represents the mortality effects of daily variations in the complex urban air pollution mixture or an unknown toxic entity than the metrics of PM used in the analyses. Some caution is, however, needed in drawing conclusions about the analysis of PM estimates because it only reflects a subset of the available studies on PM. Whether the results are a feature of the subset of studies examined is unclear, and formal meta-analysis of the full body of PM estimates, similar to the current review, is warranted. This may provide further insights into whether the different fractions/components of PM might show different sensitivity to adjustment for NO_2.

Our results for PM are in contrast with the predominant views in the literature: although confounding of the PM-mortality associations by NO_2 has been observed in some time-series studies[25–27] and noted in reviews,[6] the general consensus is that the PM-mortality estimates are robust to adjustment for co-pollutants.[6] The associations have been regarded as reflecting a causal relationship, and experimental evidence has been used to support this. There is a lack of experimental evidence for NO_2 at current ambient concentrations and for cardiovascular endpoints, and this has contributed to uncertainty regarding whether NO_2 is causally related to health.

We also found evidence of high heterogeneity between the geographic specific summary estimates of NO_2, which suggests that it cannot be assumed that the results for one city (region) represent the results for all cities (regions). For all-cause mortality and 24-hour NO_2, the high heterogeneity between WHO region-specific estimates was completely removed after control for PM (I^2 from 66.9% to 0%), suggesting that some study estimates were a bit extreme in comparison with others in the meta-analysis, but were less so after adjustment for PM. Geographical variation in effect estimates may be due to variations in population characteristics and in pollution sources, mixtures and ambient concentrations. However, none of the variables used to represent the pollution and meteorological environments in the cities examined accounted for the high between-study variability we observed. Further work is therefore required to investigate potential explanations for the heterogeneity.

Results from the studies published since our literature search cut-off are summarised and discussed in the online supplementary appendix 1. The studies indicate that, in general, the associations between NO_2 and mortality and hospital admissions remain after control for PM. This is in keeping with the findings set out in this paper.

In addition to the issue of confounding, studies have examined the potential for factors (eg, season, socioeconomic status, age, etc) to modify the relationship between daily NO_2 and mortality or hospital admissions. Few studies have, however, examined modification of the associations of NO_2 with health by particulate air pollution. The available evidence suggests that the size of an NO_2 association may be dependent on concentrations of PM_{10}.[25] However, studies have also observed the potential for daily NO_2 to modify the relationship between PM and mortality.[28] The few available data on this issue come largely from the USA and Europe, but interaction between NO_2 and PM (on cardiac hospitalisation) has also been observed in Hong Kong.[29] Further research on this aspect of the NO_2–PM issue is needed.

Our review supports the conclusions of recent narrative reviews,[7 8] but also provides meta-analytical estimates based on two-pollutant model estimates of NO_2 from the worldwide data. Taken together with the recent quantitative reviews of cohort studies on long-term exposure to NO_2 and mortality,[30 31] and of short-term exposure to NO_2 and respiratory symptoms in children with asthma from panel studies,[8 32] the evidence suggests a need for re-evaluation of the approach to health risk assessment (hazard identification and health impact assessment) for air pollution, an activity that has long been dominated by PM.[33] The current review suggests that the relationship between temporal variations in PM and mortality may not be as robust to control for NO_2 as previously thought. We note also that attenuation of PM–mortality estimates following control for NO_2 has been observed in long-term exposure studies.[34 35] These findings could have implications for the calculation of health impacts attributable to these pollutants and for possible double counting of effects.

In summary, we identified evidence of associations between NO_2 and adverse health outcomes that are independent of PM mass. However, there was limited evidence on adjustment of the NO_2 associations for primary combustion particles that are thought to be responsible for the NO_2 associations. Therefore, some uncertainty remains regarding possible confounding and health impact assessments should reflect this.

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REFERENCES

1. Schwartz J. Particulate air pollution and daily mortality: a synthesis. *Public Health Rev* 1991–1992;19:39–60.
2. Schwartz J. Air pollution and daily mortality: a review and meta-analysis. *Environ Res* 1994;64:36–52.
3. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? *J Air Waste Manage Assoc* 1996;46:927–39.
4. Lippmann M. Human health risks of airborne particles: historical perspective. In: Schneider T, ed. *Air pollution in the 21st century—priority issues and policy. Studies in environmental science*. Vol 72. The Netherlands: Elsevier, 1998:49–85.
5. Anderson HR. Air pollution and mortality: a history. *Atmos Environ* 2009;43:142–52.
6. U.S. EPA. *Final report: Integrated Science Assessment for Particulate Matter*. Washington DC: U.S. Environmental Protection Agency, EPA/600/R-08/139F, 2009 http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=216546&CFID=39659091&CFTOKEN=38401757 (accessed Dec 2015).
7. U.S. EPA. *Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (Second External Review Draft, 2015)*. Washington DC: U.S. Environmental Protection Agency, EPA/600/R-14/006. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=288043 (accessed Dec 2015).
8. World Health Organization (WHO) Regional Office for Europe. *Review of Evidence on Health Aspects of Air Pollution—REVIHAAP Project: final technical Report*. 2013. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report, (accessed Dec 2015).
9. Health Protection Agency (HPA). *Report of a Workshop to Identify Needs for Research on the Health Effects of Nitrogen Dioxide—London, 2–3 March 2011. HPA-CRCE-026*. 2011. http://www.hpa.org.uk/Publications/Radiation/CRCEScientificAndTechnicalReportSeries/HPACRCE026/ (accessed Dec 2015).
10. Committee on the Medical Effects of Air Pollutants (COMEAP). Statement and supporting papers on Quantification of the Effects of Long-term Exposure to Nitrogen Dioxide on Respiratory Morbidity in Children. 2009. http://webarchive.nationalarchives.gov.uk/20140505104658/http://www.comeap.org.uk/documents/statements/39-page/linking/86-quantification-of-the-effects-of-long-term-exposure-to-nitrogen-dioxide (accessed Dec 2015).
11. Seaton A, Dennekamp M. Hypothesis: ill health associated with low concentrations of nitrogen dioxide—an effect of ultrafine particles? *Thorax* 2003;58:1012–15.
12. Mills IC, Atkinson RW, Kang S, *et al*. Quantitative systematic review of the associations between short-term exposure to nitrogen dioxide and mortality and hospital admissions. *BMJ Open* 2015;5:e006946.
13. Anderson HR, Atkinson RW, Bremner SA, *et al*. *Quantitative Systematic Review of Short Term Associations Between Ambient Air Pollution (Particulate Matter, Ozone, Nitrogen Dioxide, Sulphur Dioxide and Carbon Monoxide), and Mortality and Morbidity*. Report to the United Kingdom Department of Health, 2007. https://www.gov.uk/government/publications/quantitative-systematic-review-of-short-term-associations-between-ambient-air-pollution-particulate-matter-ozone-nitrogen-dioxide-sulphur-dioxide-and-carbon-monoxide-and-mortality-and-morbidity (accessed Jun 2015).
14. Atkinson RW, Kang S, Anderson HR, *et al*. Epidemiological time series studies of $PM_{2.5}$ and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax* 2014;69:660–5.
15. DerSmionian R, Liard N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
16. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al*. Assessing heterogeneity in meta-analysis: Q Statistic or I^2 Index? *Psychol Methods* 2006;11:193–206.
17. Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2015. http://handbook.cochrane.org/ (accessed Apr 2015).
18. Burnett RT, Stieb D, Brook JR, *et al*. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. *Arch Environ Health* 2004;59:228–36.
19. Samoli E, Aga E, Touloumi G, *et al*. Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. *Eur Respir J* 2006;27:1129–38.
20. Stieb DM, Judek S, Burnett RT. Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. *J Air Waste Manag Assoc* 2002;52:470–84.
21. Stieb DM, Judek S, Burnett RT. Meta-analysis of time-series studies of air pollution and mortality: update in relation to the use of generalized additive models. *J Air Waste Manag Assoc* 2003;53:258–61.
22. Committee on the Medical Effects of Air Pollutants (COMEAP). Cardiovascular Disease and Air Pollution. 2006. http://www.gov.uk/government/collections/comeap-reports (accessed Nov 2015).
23. U.S. EPA. *Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (Final Report)*. Washington DC: U.S. Environmental Protection Agency, EPA/600/R-08/071, 2008. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=194645, (accessed Dec 2015).
24. Clean Air Scientific Advisory Committee (CASAC). Review of the EPA's Integrated Science Assessment for Oxides of Nitrogen—Health Criteria (First External Review Draft—November 2013). http://yosemite.epa.gov/sab/sabproduct.nsf/15E4619D3CD3409A85257CF30069387D/$File/EPA-CASAC-14-002+unsigned.pdf, (accessed Apr 2015).
25. Katsouyanni K, Touloumi G, Samoli E, *et al*. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology* 2001;12:521–31.
26. Wong CM, Vichit-Vadakan N, Kan H, *et al*. Public health and air pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality. *Environ Health Perspect* 2008;116:1195–202.
27. Brook JR, Burnett RT, Dann TF, *et al*. Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. *J Expo Sci Environ Epidemiol* 2007;17(Suppl 2):S36–44.
28. Katsouyanni K, Samet J, Anderson HR, *et al*. *Air Pollution and Health: a European and North American Approach (APHENA). HEI Research Report 142*. Boston, MA: Health Effects Institute, 2009.
29. Yu IT, Qiu H, Wang X, *et al*. Synergy between particles and nitrogen dioxide on emergency hospital admissions for cardiac diseases in Hong Kong. *Int J Cardiol* 2013;168:2831–6.
30. Faustini A, Stafoggia M, Colais P, *et al*. Air pollution and multiple acute respiratory outcomes. *Eur Respir J* 2013;42:304–13.
31. Hoek G, Krishnan RM, Beelen R, *et al*. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ Health* 2013;12:43.
32. Weinmayr G, Romeo E, De Sario M, *et al*. Short-term effects of PM_{10} and NO_2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. *Environ Health Perspect* 2010;118:449–57.
33. Maynard RL. The effects on health of ambient particles: time for an agonizing reappraisal? *Cell Biol Toxicl* 2015;31:131–47.
34. Cesaroni G, Badaloni C, Gariazzo C, *et al*. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect* 2013;121:324–31.
35. Jerrett M, Burnett RT, Beckerman BS, *et al*. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med* 2013;188:593–9.

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